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C.O'Brien, C. Mahoney, W.J. Tharion, I.V. Sils, J.W. Castellani

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Thermal and Mountain Medicine Division
U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

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Dietary tyrosine benefits cognitive and psychomotor performance during body cooling☆

Catherine O'Brien [a,*], Caroline Mahoney [b], William J. Tharion [c], Ingrid V. Sils [a], John W. Castellani [a]

[a] *Thermal and Mountain Medicine Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760, USA*
[b] *Science and Technology Directorate, Natick Research and Development Center, Natick, MA 01760, USA*
[c] *Biophysics and Biomedical Modeling Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760, USA*

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Abstract

Supplemental tyrosine is effective at limiting cold-induced decreases in working memory, presumably by augmenting brain catecholamine levels, since tyrosine is a precursor for catecholamine synthesis. The effectiveness of tyrosine for preventing cold-induced decreases in physical performance has not been examined. This study evaluated the effect of tyrosine supplementation on cognitive, psychomotor, and physical performance following a cold water immersion protocol that lowered body core temperature. Fifteen subjects completed a control trial (CON) in warm (35 °C) water and two cold water trials, each spaced a week apart. Subjects ingested an energy bar during each trial; on one cold trial (TYR) the bar contained tyrosine (300 mg/kg body weight), and on the other cold trial (PLB) and on CON the bar contained no tyrosine. Following each water immersion, subjects completed a battery of performance tasks in a cold air (10 °C) chamber. Core temperature was lower ($p=0.0001$) on PLB and TYR (both 35.5±0.6 °C) than CON (37.1±0.3 °C). On PLB, performance on a Match-to-Sample task decreased 18% ($p=0.02$) and marksmanship performance decreased 14% ($p=0.002$), compared to CON, but there was no difference between TYR and CON. Step test performance decreased by 11% ($p=0.0001$) on both cold trials, compared to CON. These data support previous findings that dietary tyrosine supplementation is effective for mitigating cold-induced cognitive performance such as working memory, even with reduced core temperature, and extends those findings to include the psychomotor task of marksmanship.

Keywords: Hypothermia; Marksmanship; Working memory

1. Introduction

Stressful conditions that elevate brain catecholamine activity, such as cold or heat stress, altitude exposure, and tail shock in animals, are often associated with decreased cognitive performance [1–4]. One reason may be depletion of central catecholamines, since both norepinephrine [5] and dopamine [6,7] are important for acquiring and performing cognitive and motor skills. Catecholamines serve as neurotransmitters, so augmenting the availability of the amino acid tyrosine, the precursor for catecholamine synthesis, through dietary supplementation could help maintain brain function by sustaining brain neurotransmitter levels [8]. Tyrosine and other neutral amino acids are competitive binders to the transport receptor for crossing the blood brain barrier, therefore, when there is a higher ratio of tyrosine relative to total neutral amino acids the rate of tyrosine transport will increase [9]. Under stressful conditions that activate tyrosine hydroxylase, the rate-limiting enzyme that catalyzes the conversion of tyrosine to L-dopa, the enzyme becomes more responsive to increased intraneural tyrosine, whether through ingestion or injection of tyrosine [9,10]. Animal studies have

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* Corresponding author. Thermal and Mountain Medicine Division, U.S. Army Research Institute of Environmental Medicine, Kansas Street, Building 42, Natick, MA 01760-5007, USA. Tel.: +1 508 233 5973; fax: +1 508 256 5298.

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demonstrated that supplemental tyrosine increases brain levels of norepinephrine [2,4,11] and dopamine [10].

Soldiers are required to perform missions even at environmental extremes; therefore, identification of effective countermeasures to mitigate performance degradation due to environmental stress is important. One example is the 1995 hypothermia deaths of four Ranger students, where poor decision-making may have contributed to prolonged cold water immersion [12]. Both animal and human studies provide evidence that supplemental tyrosine is effective at limiting cold-induced decreases in cognitive performance [5,11,13,14]. In humans, Banderet and Lieberman [13] found supplemental tyrosine was effective at decreasing symptoms such as headaches, cold sensation, and fatigue during a combined stress of cold and hypoxia. Performance on cognitive tests, including addition, coding, map/compass, pattern recognition, and reaction time was also better with tyrosine, compared to placebo. Shurtleff and Thomas [14] found that tyrosine offset the 30% reduction in performance on a Match-to-Sample test that involves short-term working memory after 60 min cold (4 °C) air exposure. Tyrosine had no effect during a 22 °C control condition, suggesting that tyrosine availability only became important during the cold condition when there was increased firing of catecholaminergic neurons. While these studies provide evidence for the effectiveness of tyrosine supplementation in a cold environment, none of the human studies used a cold stress that was sufficient to reduce core temperature. Furthermore, no studies have evaluated the effect of tyrosine supplementation on physical performance during cold stress.

The purpose of the present study was to evaluate the effect of tyrosine supplementation on cognitive, psychomotor, and physical performance during cold air exposure following a stressful repeated cold water immersion protocol that induces mild hypothermia [15]. Based on previous studies, it was hypothesized that cold-induced cognitive performance decrements would be mitigated with tyrosine. Marksmanship performance has been previously demonstrated to be sensitive to environmental stressors [16,17], therefore, it was hypothesized that decrements in performance on this psychomotor task would also be mitigated with tyrosine. A secondary aim of this study was to identify physical performance tasks that are sensitive to body core cooling, and whether tyrosine reverses any observed physical performance decrements.

2. Materials and methods

This protocol was approved by the U.S. Army Research Institute of Environmental Medicine Scientific and Human Use Review Committees. Written informed consent was obtained from each person who volunteered to participate after being informed of the purpose, experimental procedures, and known risks of the study. Investigators adhered to U.S. Army Regulation 70-25 and U.S. Army Medical Research and Materiel Command Regulation 70-25 on the Use of Volunteers in Research. The volunteers were enlisted Soldiers. Their physical characteristics were age 20±2 years, height 174±7 cm, weight 76±11 kg, body fat 19±6%, and VO_{2peak} 48±8 ml/kg/min.

2.1. Experimental design

Fourteen men and one woman completed a control trial (CON) in warm (35 °C) water, then, with one week between trials and in counter-balanced design, two trials in cold water (temperature based on each subject's body composition to induce a fall in rectal temperature from 37 °C to 35 °C in 90 min) [18]. Each cold trial consisted of a 90-min chest-deep (arms not immersed) water immersion, a rewarming period during which the subject was immersed in warm water until their core temperature returned to its initial value, then a second 90-min cold water immersion followed by ~40 min in 19 °C air. At that time the subject changed into dry clothes and entered the cold air chamber where the performance tests were conducted, at approximately 1330 h. On CON the schedule was the same, except the subjects did not undergo rewarming since they had not been cooled. On each trial the subject consumed an energy bar (285 kcal) upon arrival at the laboratory at approximately 0730 h and again during the period between cold water immersions at approximately 1130 h. On one cold water trial (TYR) the energy bar contained tyrosine (each dose 150 mg/kg body weight), whereas on the other cold water trial (PLB) and on CON, the bar was a placebo containing no tyrosine. The bars were developed by food scientists to be matched for taste and texture to ensure that subjects would not know whether they were receiving tyrosine or placebo. The two cold water trials were conducted in a double-blind manner and the code only broken after all subjects had completed testing.

2.2. Measurements

Body composition was determined by skinfold measurements at four sites (biceps, triceps, suprailiac, and subscapular), using the equation of Durnin and Wormersley [19]. Fitness level (VO_{2peak}) was determined using an incremental cycle ergometer test. On the morning of a trial, the subjects placed a rectal temperature probe (ESO-1; Physiotemp Instruments, Inc., Clifton, NJ) 10 cm past the anal sphincter, and skin thermistors (Concept Engineering, Old Saybrook, CT) were attached at 11 skin sites: foot, calf, medial thigh, lateral thigh, chest, triceps, anterior aspect of the forearm, subscapular, forehead, dorsal hand, and the dorsal middle phalange of the middle finger. Mean weighted skin temperature was calculated as $T_{sk}=0.06T_{foot}+0.17T_{calf}+0.28T_{thigh}+0.14T_{chest}+0.07T_{tricep}+0.07T_{forearm}+0.14T_{subscapular}+0.07T_{hand}$.

2.3. Performance battery

The U.S. Special Operations Command (SOCOM) uses a standardized set of tests to evaluate cognitive [20] and physical performance [21] under a variety of stressful conditions. These tests were chosen by their relevance to mission requirements, the accuracy and reproducibility of the measurements, and the time and equipment required for administration of the tests. The performance tests were administered on each trial in a cold air (10 °C) chamber to limit rewarming, and they were completed in order of increasing metabolic activity in order to maintain

reduced body temperature as long as possible. The cognitive tests were completed first, followed by weapon disassembly/reassembly, marksmanship, hand grip strength and endurance, pull-ups, and step test. Due to spatial constraints, the SOCOM marksmanship task was replaced by one that has been previously used in environmental extremes [16,17]. Five familiarization sessions were completed at a neutral room temperature for each task before testing began. A self-paced cycle ergometer test was added to the protocol after the first few subjects had completed testing. Eleven of fifteen subjects performed this task, which was practiced on three occasions before testing began. This task was not part of the SOCOM battery.

2.4. Cognitive tests

The computer-based cognitive tests are described in detail by Thomas and Schrot [20]. Match-to-Sample evaluates short-term spatial memory and pattern recognition. Upon subject initiation, an 8×8 matrix appears with a random pattern of red or green squares. After 3 s, the screen blanks for either a short (1 s) or long (15 s) delay, after which two matrices appear, only one of which matches the original (the other differing in one or two of the 64 squares). Time to make a response and which matrix is chosen are recorded. Completion of 20 trials takes ~5 min. Complex Reaction Time displays a set of boxes in the same orientation as the four arrow keys on the keyboard. A red square appears randomly in a box, and the subject must press the corresponding arrow key, after which the red square immediately appears in another square. Completion of 60 presentations takes ~1 min. Response time and accuracy are measured. Visual Vigilance evaluates sustained visual attention and choice reaction time. Letters or numbers appear briefly (0.5 s) in the center of the screen, with random delays (1–5 s) between presentations. The subject must press the down-arrow when only "A" or "3" appear. This task takes ~6 min for 100 presentations. Serial Addition/Subtraction measures the ability to perform simple calculations. Two digits are presented with either a plus or minus sign. If the answer is positive, the last single digit of the answer is to be entered. If the answer is negative, the subject must add 10 and then enter the resulting single positive number. This task takes ~2 min for 50 presentations. Logical Reasoning measures general reasoning ability using true or false statements about the sequence of two letters presented on the screen, "AB" or "BA." The statements are positive/negative and active/passive, and refer to whether one letter precedes or follows the other. This task takes ~3 min for 32 presentations. Repeated Acquisition assesses the subject's ability to learn, decode, or acquire a key press sequence. Twelve blocks are presented and the subjects must learn the sequence of up, down, right, or left arrow keys by trial and error over 15 total presentations. This task takes ~8 min.

2.5. Psychomotor tests

Two psychomotor tasks were administered. One was disassembly and reassembly of an M-16 rifle (12 steps), with total time recorded. The other task was rifle marksmanship speed and accuracy, measured using a single stationary target laser system (Noptel, Oulu, Finland). Subjects waited with the rifle below waist level, then took their shot after a red LED light appeared at a random interval (1–10 s). Three sets of five shots fired from a standing position on a target simulating 46 cm at a distance of 50 m were analyzed. Calculated parameters included Distance from Center of Mass (DCM, mm), which is the distance between the average of a five shot series from the center of the target; Shot Group Tightness (SGT, mm^2), which is the area in which the five shots are clustered; Horizontal SGT and Vertical SGT (mm), which represent the spread of the five shots in each direction; Horizontal Deviation and Vertical Deviation (mm), which represent the average directional deviation of the five shots from the center of the target, with a negative value indicating left or below the target; and Sighting Time (min), which is the time the red LED light appears until the trigger is pulled. This task took ~2 min.

2.6. Physical performance tests

The physical performance tasks are described in detail by Valaik et al. [21]. Hand grip strength was measured in both hands on three maximal efforts, followed by a measure of handgrip endurance. Because tissue cooling can affect muscle strength, the hand grip endurance test used the force determined as 50% of the average maximum grip strength obtained during the last practice session (normal room temperature). Thus, even if cold stress on any trial altered maximum grip strength, grip endurance was still measured at the same absolute force. Hand grip strength and endurance took ~5 min. Pull-ups were performed from a hanging position with knees bent. The maximum number of pull-ups (full arm extension to chin over the bar) was recorded. A single step test was performed while wearing a 20 kg weighted vest. Subjects were instructed to complete as many steps (up with both feet and down with both feet counting as one step) as possible in 1 min. Immediately following the step test, subjects completed a self-paced cycle ergometer test of a fixed amount of work (3 kJ per kg body weight). The initial work rate was set for each subject to reflect a 50% VO_2 peak exercise intensity at a pedal cadence of 60 rpm, but the subjects could thereafter alter the work rate according to their preference throughout the test. Subjects were instructed to complete the task as quickly as possible. The cycle ergometer test was practiced on three occasions before testing began.

2.7. Statistical analyses

Data were analyzed across all three trials using repeated measures analysis of variance. Tukey's Honestly Significant Difference (HSD) post-hoc test was applied when significant main effects were found. Statistical significance was set at $p<0.05$. Because of the large number of performance test analyses (27), there is an increased probability of a Type I error, i.e., finding significant differences when they do not exist. A Bonferroni correction to account for the large number of analyses would require a statistical significance level of $p<0.001$ in order to maintain the designated $p<0.05$ level of statistical significance after the correction was applied. In the

present study, a variety of performance tasks were administered in order to find out where tyrosine might be effective as a countermeasure, therefore, to avoid an increase in the probability of Type II errors, the Bonferroni correction was not used. However, actual p values are presented, and the physiological significance of differences can be evaluated in each case. All data are presented as mean±standard deviation.

3. Results

Men and women have similar responses to CWI after adjustment for body fat and size [22], therefore, females were not excluded from participation. The data from the single female subject in this study fell within the range of the male subjects and her data has been included in the analysis.

A typical response of rectal, mean skin, and finger temperatures during cold air exposure is shown in Fig. 1 to demonstrate the effect of cold air exposure and temperature changes as activity increased with the performance tasks. The cold water immersions reduced rectal temperature ($F(2,28)=131.01$, $p<0.0001$) by ~1.5 °C in both PLB (35.5±0.6 °C) and TYR (35.4±0.5 °C) trials, which were significantly different ($p<0.05$, Tukey's HSD) from CON (37.1±0.3 °C), but not from each other. During cold air exposure, mean skin temperature was lower ($F(2,28)=23.286$, $p<0.0001$) on PLB (25.4±1.6 °C) and TYR (25.4±1.5 °C) trials, which were significantly different from CON (27.7±1.4 °C, $p<0.05$), but not from each other. The minimum finger temperature achieved during cold air exposure was significantly lower ($F(2,28)=5.9023$, $p=0.0073$) on the PLB trial (14.7±1.4 °C), compared to CON (16.0±2.0 °C, $p<0.05$); but TYR (15.0±1.4 °C) was not significantly different from either CON or PLB.

3.1. Cognitive performance

Data from the cognitive performance tests are shown in Table 1. Note that statistical significance is only presented relative to CON because Tukey's HSD post-hoc analysis did not indicate statistical significance between PLB and TYR for any variable. Cold water immersion reduced ($F(2,28)=4.3470$, $p=0.023$) the percentage of correct answers on the Match-to-Sample test during the PLB trial for an 18% reduction in performance. Response time was 10% slower ($F(2,28)=5.6968$, $p=0.0084$) during the PLB trial for the Addition/Subtraction test. Response time on the Vigilance test improved ($F(2,28)=5.4199$, $p=0.010$) on both cold trials by 25%–38%, compared to CON.

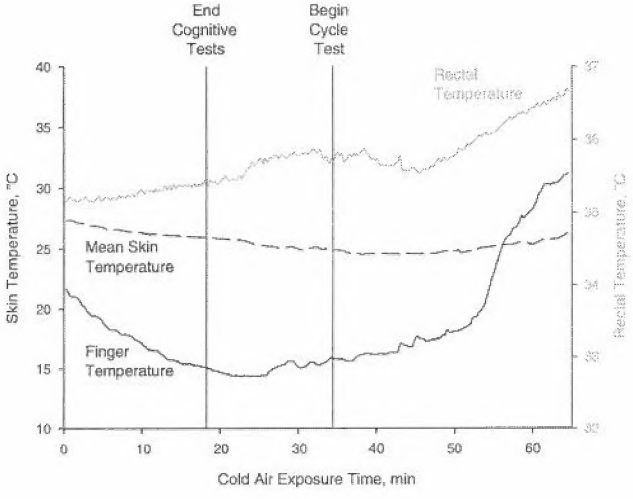

Fig. 1. Mean skin and finger skin temperatures (left hand axis) and rectal temperature (right hand axis) during cold air exposure for a representative subject.

Table 1
Cognitive performance following resting cold water immersion

	Control	Placebo	Tyrosine
Match-to-Sample, % correct	67±15	55±15 *	62±14
Response time, s	3.7±0.8	3.3±1.1	3.3±1.1
Complex Reaction Time, % correct	91±11	89±9.8	89±13.5
Response Time, s	0.38±0.06	0.40±0.06	0.41±0.07
Addition/subtraction, % correct	94±9	93±6	93±7
Response Time, s	2.0±0.6	2.2±0.8 *	2.1±0.8
Vigilance, % correct	92±7	96±10	92±8
Response time, s	0.08±0.02	0.05±0.03 *	0.06±0.02 *
Grammatical reasoning, % correct	82±17	84±15	79±19
Response time, s	3.2±1.3	2.9±1.2	3.2±1.6
Repeated Acquisition, % correct	71±12	70±14	72±12
Response time, s	9.9±3.3	9.4±2.7	9.7±2.5

Data are presented as mean±standard deviation.
* Tukey's HSD post-hoc, $p<0.05$ compared to Control.

3.2. Psychomotor and physical performance

Data from the physical performance tests following resting cold water immersion are shown in Table 2, with marksmanship parameters presented in Table 3. Note again that statistical significance is only presented relative to CON because Tukey's HSD post-hoc analysis did not indicate statistical significance between PLB and TYR for any variable. The only physical performance measures affected by cold were marksmanship (DCM, $F(2,28)=6.868$, $p=0.004$; SGT, $F(2,28)=6.196$, $p=0.006$; Vertical SGT, $F(2,28)=4.117$, $p=0.027$); and step test ($F(2,28)=23.592$, $p<0.0001$). Marksmanship performance decreased by 14% on the PLB trial, compared to CON, but there was no significant difference between the TYR and CON for any parameter. On the PLB trial, the poorer marksmanship scores were due to increased shot dispersion and, more specifically, in the

Table 2
Physical performance following resting cold water immersion

	Control	Placebo	Tyrosine
Weapon assembly, s	103±25	107±27	114±33
Grip strength, RH, kg	42±5	41±6	42±5
Grip endurance, RH, s	68±16	58±27	56±23
Grip strength, LH, kg	43±5	42±7	43±5
Grip endurance, LH, s	65±22	64±24	61±27
Pull-ups	10±5	9±5	9±5
Steps	53±5	47±6 *	47±7 *
Cycle test, s†	1394±158	1449±179	1458±199

Data are presented as mean±standard deviation.
* Tukey's HSD post-hoc, $p<0.05$ compared to Control. †$n=11$.

Table 3
Marksmanship performance following resting cold water immersion

	Control	Placebo	Tyrosine
Distance from center of mass, mm	4.7±0.9	5.9±1.2*	5.3±1.2
Shot Group Tightness, mm^2	59±20	100±46*	77±30
Horizontal Shot Group Tightness, mm	7.8±2.2	9.4±2.3	8.2±2.2
Vertical Shot Group Tightness, mm	7.6±1.7	10.2±2.8*	9.1±2.5
Horizontal Deviation, mm	−0.3±1.8	−0.2±2.5	0.1±2.5
Vertical Deviation, mm	−0.7±1.8	−0.2±1.5	−0.7±1.8
Sighting Time, s	6.4±2.1	7.0±2.4	7.0±2.0

Data are presented as mean±standard deviation.
* Tukey's HSD post-hoc, $p<0.05$ compared to Control.

vertical direction. Step test performance was reduced by 11% on both PLB and TYR trials, compared to CON.

4. Discussion

Physiological stressors such as cold exposure that cause sustained increases in brain catecholamine turnover have been associated with decreases in working memory, and these decrements in performance have previously been shown to be offset by dietary tyrosine administration [14]. This was confirmed in the present study, where tyrosine ingestion mitigated the decrease in performance on the Match-to-Sample test during cold exposure that was observed with placebo in subjects with reduced core temperature. This study is the first to extend those observations to a more practical demonstration of the effectiveness of tyrosine supplementation for mitigating the cold-induced decrease in psychomotor performance, as indicated by marksmanship.

Marksmanship requires cognitive decision-making to determine the optimal time to take a shot, and motor control for physical steadiness required to support the weapon and for control of breathing. Brain catecholamines are important for both cognitive skills and motor control [5–7], as well as for attention regulation and inhibition of distracting stimuli, both of which would be important for marksmanship skills in a cold environment [23]. If brain catecholamine activity during cold exposure is enhanced by supplemental tyrosine, this could contribute to improved marksmanship performance. Support for this mechanism is provided by data in rats, which maintained higher brain norepinephrine levels during cold exposure with tyrosine, compared to a placebo trial, and the rats treated with tyrosine exhibited improved behavioral performance [11].

The marksmanship procedure used in the present study has previously been demonstrated to be sensitive to a variety of environmental stressors, including hypoxia [16] and operational stress in a cold–wet environment [17], and was sensitive to the cold exposure in the present study where core temperature was reduced, but upper body tissues were not directly pre-cooled. Other methods of marksmanship evaluation, such as a small arms simulator and use of moving targets, have not demonstrated a decrease in marksmanship performance due to thermal strain (heat or cold) [24]. One reason for the discrepant findings regarding cold effects on marksmanship may be the degree of thermal strain induced, since the cold stress used by Tikuisis et al. [24] did not reduce core temperature. In another study, Reading et al. [25] used a similar marksmanship system as the present study to evaluate performance after a 2 h cold air (4 °C) exposure and found no change due to cold exposure, but their findings appear to have been confounded by development of a learning effect in those subjects. Our study observed poorer vertical shot group tightness with body cooling during the PLB trial, suggesting vertical stabilization as a potential intervention to improve marksmanship in the cold through the use of rifle supports such as sandbags. This may be another reason no difference in marksmanship performance was found by Tikuisis et al. [24], since those subjects fired from a prone position using sandbags.

Memory registration is typically a cognitive task that is affected early in body cooling. Deficits in memory have been observed even with small reductions in core temperature (e.g., as little as 0.5 °C) [26]. Shurtleff et al. [14] even found decrements with a cold air exposure (4 °C for 60 min) that would probably not have reduced core temperature at all, although that cold air exposure was stressful enough to cause a significant increase in plasma norepinephrine levels. Supplemental tyrosine limited the decrease in Match-to-Sample performance under those conditions [14], and our data confirm these findings. Furthermore, our data are the first to demonstrate that tyrosine is an effective countermeasure against cognitive deficits associated with larger decreases in core temperatures.

A secondary goal of the present study was to identify which physical performance tasks were sensitive to body cooling. The only physical performance task affected by cold exposure in the present study was the step test. The impairment in that task was probably due to local tissue cooling produced by cold water immersion in addition to the lowered core temperature. Decreased muscle, nerve, and joint temperatures that occur with direct tissue cooling (e.g., cold water immersion) impair physical performance [1,27]. Although tissue cooling may have persisted at the beginning of the cycle ergometer test, it is likely that continued activity increased muscle blood flow more than during the step test, probably restoring tissue temperatures to near normal. Physical performance in upper body tasks was unaffected by lowered core temperature.

The tyrosine dose used in the present study (150 mg/kg body weight) is typical of most of the human and animal studies; however, little research has been done to determine an optimal dose. Banderet and Lieberman [13] report plasma tyrosine levels of 109 nmol/ml 150 min after ingestion of 100 mg/kg body weight. Glaeser et al. [28] measured plasma tyrosine concentration for 8 h after both 100 and 150 mg/kg body weight doses, and found plasma tyrosine peaked after 2 h with both doses (154 and 203 nmol/ml, respectively), but only remained elevated after 8 h with the higher dose. For extended cold exposure, the higher dose would seem more appropriate. Badawy and Williams [29] looked at brain dopamine and norepinephrine levels after intraperitoneal tyrosine doses ranging from 5–500 mg/kg body weight, and found the largest elevation in catecholamines at a tyrosine dose of only 20 mg/kg body weight. They suggest that negative feedback mechanisms and/or substrate inhibition of tyrosine hydroxylase could explain the lowered level of catecholamine synthesis despite

increased elevation of brain tyrosine. Another question raised by Anisman and Zacharko [30] is how stressors may condition or sensitize the neurotransmitter pathways. For example, repeated exposure to a stressor may increase tyrosine hydroxylase activity, resulting in restored concentration of catecholamines without the need for supplemental tyrosine. Further research is required to produce a dose-response curve for brain catecholamine synthesis following tyrosine supplementation in humans, and to determine whether this relationship is modified by different stressful conditions, by prior exposure to the stressor, or by changes in sensitivity to exogenous tyrosine.

This study supports previous research demonstrating the effectiveness of tyrosine supplementation for mitigating cold-induced cognitive performance decrements such as working memory and extends those findings to include performance on the psychomotor task of marksmanship. The proposed mechanism for this relationship makes the assumption that the reduced brain catecholamine level associated with stressful conditions such as cold exposure is responsible for the degraded cognitive performance, and that elevating tyrosine levels increases tyrosine hydroxylase activity, thereby restoring brain catecholamine levels. However, tyrosine hydroxylase activity may be regulated in a number of ways beyond simply increased tyrosine availability. Future studies could be done to provide further support for the proposed hypothesis. For example, control studies may include administering amino acids that compete with tyrosine uptake, which should reduce the beneficial effects of tyrosine on cognitive performance, or administering amino acids that are precursors to pathways other than catecholamine synthesis. Nonetheless, tyrosine supplementation would appear to be a beneficial countermeasure for cognitive and psychomotor performance during cold strain, and may be expected to be effective under other stressful conditions, including heat stress and altitude exposure. Future studies should also consider whether multi-stressor conditions, such as those Soldiers experience during sustained operations involving environmental stress, physical and mental fatigue, sleep deprivation and caloric restriction, would also benefit from tyrosine supplementation.

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